

The Examiner rejected claims 1-16 and 18-20 under 35 U.S.C. § 103(a) as unpatentable over Nicoll et al., Journal of Gastroenterology and Hepatology, vol. 12, pp. 843-854 (1997) ("Nicoll"). In support of the rejection, the Examiner commented that Nicole discloses the nucleoside analog "adefovir," and discloses that adefovir has been shown to increase the activity of natural killer cells and stimulate immune responsiveness, most likely through endogenous interferon- $\alpha$  production.

The Examiner acknowledged that Nicoll does not disclose a combination therapy of adefovir with interferon- $\alpha$ , and also does not disclose the 26 week protocol used in the present claims. The Examiner concluded that it would have been obvious to administer adefovir in combination with interferon- $\alpha$  for the treatment of hepatitis B virus, in light of the comment that adefovir may stimulate immune responsiveness through endogenous interferon- $\alpha$  production. The Examiner also appears to have admitted that Nicoll fails to enable a treatment protocol of more than 26 weeks. Applicants respectfully traverse this rejection.

Claim 11, the only independent claim in this application, recites a method of treating a human patient infected with hepatitis B virus, which comprises administering to the patient both a nucleoside analog and interferon- $\alpha$  during a period of at least 26 weeks. In order to establish a *prima facie* case of obviousness of this invention, the Examiner must show, among other things, a motivation in the art to have practiced this method. For the reasons given below, one skilled in the art would not have been motivated to practice the claimed method in light of the Nicoll disclosure. If anything, Nicoll's discussions relating to possible combination therapies actually evidences an uncertainty in the art on the subject, rather than clear guidance to practice the claimed methods.

Nicoll discloses two major classes of agents for the treatment of hepatitis B: immunomodulating agents such as interferons, and direct antiviral agents such as nucleoside analogs. The article comments on the use of those agents alone, and also speculates on possible combination therapies. Many of Nicoll's comments on possible combination therapies appear, admittedly by Nicole

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herself, as only speculation. For example, the last sentence of the Abstract states that "[i]n this article, we . . . speculate on promising approaches with combination chemotherapy . . . ." Furthermore, at the end of the article at page 850, Nicoll concludes that "[t]here is not enough information to make predictions concerning combination chemotherapies." The author's conclusions in her own article thus appear to contradict the Examiner's belief that the combination therapy now claimed would have been obvious in view of the very same text.

When Nicoll does speak favorably of potential in combination therapies, she speaks in terms of combination of two nucleoside analogs, rather than a combination of interferon- $\alpha$  with a nucleoside analog. Indeed, at page 849, Nicoll cites to three prior trials of combination therapy of interferon- $\alpha$  with a nucleoside analog, and concludes that the therapy "has shown no improvement over IFN- $\alpha$  alone." Those cited treatments, incidentally, did not extend for at least 26 weeks as is done in the present methods. Nicoll goes on to say on the same page that "[t]he strategy of combining antiviral agents such as nucleoside analogs with immunomodulators may need to be reappraised," and that "combinations of two nucleoside analogs, such as famciclovir and lamivudine may be synergistic and offer more therapeutic potential." Thus, Nicoll itself appears to teach away from, not towards, a combination therapy of interferon- $\alpha$  with a nucleoside analog.

The Examiner commented that "it would not appear that tandem adefovir/interferon administration would be contraindicated since IFN levels are boosted by" adefovir. On a legal level, the test of obviousness is not whether something is "not contraindicated." Something could very well be "not contraindicated," but that is not enough to make it obvious. Instead, the person skilled in the art must have an affirmative motivation to do what the applicants have done. On a factual level, the possible action of adefovir as an interferon inducer has not led, in applicant's experience or knowledge, to documented clinical effects. Furthermore, Nicoll's own expressed doubts about combination therapy of interferon- $\alpha$  and nucleoside analogs in general appear to contradict the Examiner's belief that the combination therapy now claimed would have been

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obvious in view of the very same text. In her comments on the problems with combination therapies, Nicoll particularly made no special exception for adefovir apart from all other nucleoside analogs discussed. Furthermore, given the lack of success with other nucleoside analogs, those skilled in the art would not have had an expectation of success in using adefovir in combination with interferon- $\alpha$ .

The Examiner further commented that Nicoll fails to enable a more than 26 week treatment protocol. Applicants acknowledge that Nicoll does not suggest the claimed treatment that lasts of a period of at least 26 weeks.

The Examiner also stated that the present specification fails to enable the combination therapy of interferon- $\alpha$  and adefovir, because the working example in the specification discloses results for a patient receiving a combination therapy of interferon- $\alpha$  and lamivudine. The Examiner did not, however, reject any claims as non-enabled. The specification does enable the full scope of the claims. With regard to a possible combination therapy of interferon- $\alpha$  and adefovir specifically, the specification identifies adefovir as an example nucleoside analog, and states that it may be administered, for example, in a dose of between 5 and 30 mg per day. Specification at page 4, lines 34-35. The specification also states that interferon- $\alpha$  may be administered, for example, between 30 megaUnits and 15 megaUnits per week. Specification at page 5, lines 11-13. It would be a matter of routine for those skilled in the art to follow the guidance set forth in the specification to administer this combination therapy or any other specific type of therapy embraced by the claims.

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In light of the above, the pending claims should be in condition for allowance. Please grant any extensions of time required to enter this Response and charge any additional fees required to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: December 21, 2001

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